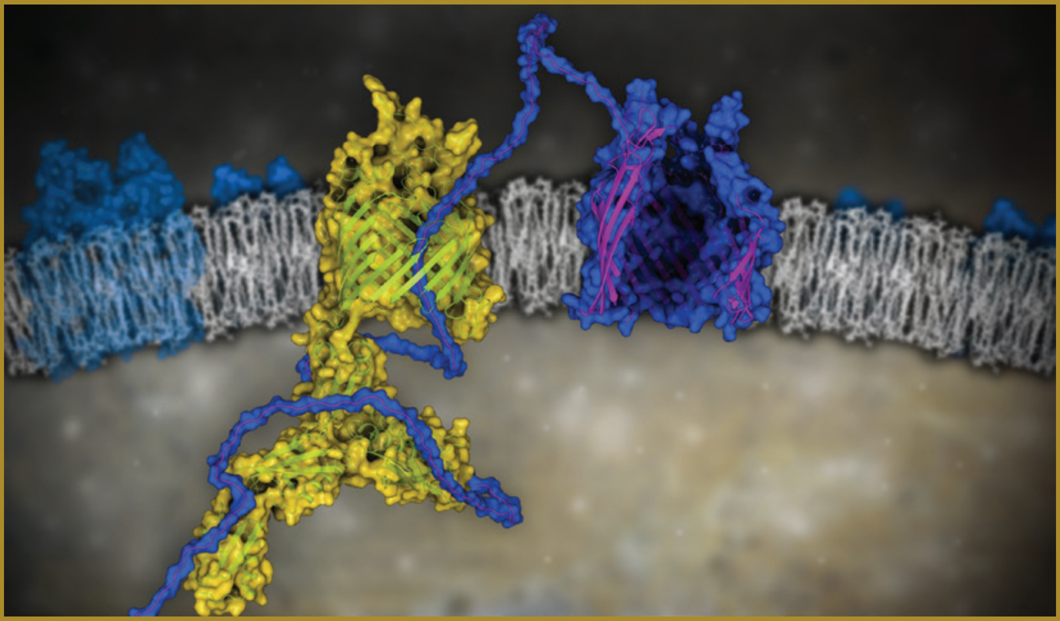


The surface of a bacterial cell is covered with a variety of proteins required for survival, including those that allow the cell to sense and interact with its environment, communicate with other cells, or evade the mammalian immune system. As described in this chapter, NIDDK researchers have determined the detailed atomic structure of the cellular machinery responsible for incorporating these essential proteins into the bacterial surface. Knowing the structure of the major assembly component (known as BamA, depicted in yellow/green) provides insight into how bacteria place proteins (blue/purple) at their surface and suggests new drug targets to combat infectious diseases.

Image provided by Dr. Nicholas Noinaj, Dr. Adam Kuszak, and Dr. Susan Buchanan, NIDDK.

Cross-Cutting Science

Medical advances are not always achieved in great, intuitive leaps. More often, new prevention strategies, treatments, and cures result from a long, gradual accumulation of new knowledge from years of scientific research. Insights into the fundamental biologic building blocks and processes of an organism—its genes, the proteins they encode, the inner workings of cells, and the ways cells communicate with each other—can have broad and far-reaching implications. Indeed, many significant advances in our knowledge of disease and disease treatment can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted. With the development of innovative scientific technologies and the emergence of new scientific disciplines as talented and creative research teams join together to tackle ever more complex challenges, new opportunities to make exciting discoveries arise each day. The insights gained through this research can be expected to further scientific progress in many research areas, for today's discoveries may hold the seeds of tomorrow's cures.

Described in this chapter are several recent studies that illustrate the Institute's commitment to basic and applied research relevant across a broad spectrum of scientific disciplines. Also featured are several NIDDK programs that demonstrate the breadth and collaborative nature of the NIDDK's research efforts, including several clinical research studies which the NIDDK is uniquely positioned to support. These studies are, for example, evaluating new uses for medications, including generic drugs; testing behavioral or lifestyle changes as a therapeutic approach; or are large studies requiring significant investment. In many cases these studies benefited from partnerships with non-federal funders but were unlikely to have been undertaken solely by these other funding sources.

The NIDDK's trans-NIH and public-private collaborations have also led to the development of cutting-edge technology, such as microbial-resistant urinary catheters, more accurate drug toxicity screening tools, important artificial pancreas technologies, and state-of-the-art biomedical imaging.

Finally, the NIDDK is dedicated to delivering important health information to the public. Through disease-specific Information Clearinghouses and other online resources, the NIDDK offers a wide variety of informational materials to health care professionals, patients and their families, and others across the country and across the world.

AGING AND THE BRAIN

Inflammation in the Brain Links Obesity and Aging: Two studies further clarified the role of brain signaling in aging and metabolic disease. This research, done in mice, suggests that decreasing inflammation in the brain may reduce the signs of aging and age-related disease. Aging involves gradual functional decline and affects many tissues and organs. However, how aging determines lifespan is poorly understood, as is why the risk of certain diseases, like type 2 diabetes, increases with age. Inflammation plays a role in type 2 diabetes and other age-related diseases, but how inflammation influences aging is unclear. The brain has emerged as a potential regulator of aging and metabolism, and therefore understanding how metabolic disease and inflammation affect the brain—and *vice versa*—are key research goals.

Toward those goals, in a recent study researchers examined the role of the hypothalamus, a region of the brain, in aging. The hypothalamus plays a key role in growth, reproduction, and metabolism. Given these important roles, researchers investigated whether the hypothalamus could also control aging and lifespan. Because previous research showed that inflammatory changes contribute to the development of metabolic syndrome, they focused on two inflammatory signaling proteins, IKK-β and NF-κB, which act together to trigger downstream inflammatory responses. The researchers found that NF-κB is more active in the hypothalamus of older mice than that of younger mice. To determine the effect of NF-κB on aging, researchers increased or decreased IKK-β/NF-κB activation in the hypothalamus of mice and evaluated age-related physiology. Mice with decreased NF-κB activation performed better on cognitive and strength tests, displayed more robust physical characteristics, and lived longer, while the mice with increased NF-κB activation performed poorly and had shorter lifespans than their normal counterparts. The effects of IKK-β/NF-κB on aging were further traced to gonadotropin-releasing hormone (GnRH), which is depleted as IKK-β/NF-κB activation increases. To test whether replenishing GnRH might reverse the effects of aging, researchers gave mice GnRH injections and found that this therapy prevented age-induced brain cell loss and reduced age-related skin, muscle, and cognitive degeneration. These results suggest that inflammatory responses in the hypothalamus orchestrate aging throughout the body and may give clues to how aging occurs and how lifespan can be increased.

In another study, several of the researchers who conducted the first study found a link between obesity-related inflammation and neurodegeneration, or loss of neuron function. They discovered that IKK-β/NF-κB signaling promoted metabolic disease by disrupting adult neural stem cells (NSCs) in the hypothalamus. NSCs are a type of stem cell; like other stem cells they are self-renewing and can develop into many different types of cells. NSCs, in particular, can become many different types of brain cells. The researchers sought to identify adult NSCs in the hypothalamus and to determine if disruption of normal NSC function plays a role in diseases such as obesity and diabetes. They found that in adult mice NSCs were particularly numerous in the hypothalamus, where they slowly produced new brain cells. A high-fat diet, however, reduced the NSCs' generation of new brain cells and prevented their development into different types of brain cells. The scientists found that increased IKK-β/NF-κB activation was responsible for these effects: reducing IKK-β/NF-κB activation promoted NSC proliferation and development into different brain cell types. Moreover, mice with increased IKK-β also developed glucose intolerance—a symptom of prediabetes and diabetes—and displayed overeating and weight gain, resulting in the onset of severe obesity. These results suggest that high-fat diets in mice are associated with inflammatory responses in the hypothalamus that can reduce the number and activity of neural stem cells, leading to neurodegeneration, obesity, and diabetes. Together, these findings in mice may provide a greater understanding of human aging and metabolism and lead to prevention or treatment strategies for obesity-related diseases, such as type 2 diabetes.

Zhang G, Li J, Purkayastha S, et al. Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH. Nature 497: 211-216, 2013.

Li J, Tang Y, and Cai D. IKKβ/NF-κB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. Nat Cell Biol 14: 999-1012, 2012.

New Insight into Alzheimer's Disease: Recent research reveals individual differences in brain tissue obtained from two patients with Alzheimer's disease who had distinct clinical histories and severity of brain damage. Alzheimer's disease is a progressive, irreversible brain disease that destroys memory and thinking skills. Many changes take place in the brain of a person with Alzheimer's disease. Some of these changes can be observed in brain tissue by using microscopy after death. A common abnormality evident in the brains of people who have died with the disorder is the amyloid plaque. The plaques consist predominantly of abnormal deposits of a protein fragment called beta-amyloid or β-amyloid, frequently abbreviated as Aβ. The molecular architecture of Aβ aggregates that develop in human brain tissue has not been characterized in detail, but scientific findings to date suggest that structural variations may be biomedically important.

For the first time, scientists precisely characterized the molecular structures of Aβ fibrils that form in the brains of patients with Alzheimer's disease. Using sophisticated biophysical techniques, a single-length predominant fibril structure was recovered from each patient; however, the fibrils were structurally different from each other. These data suggest that brain fibrils appear first at a single site and then spread to other locations in the brain while retaining their respective identical structural signatures. The study further suggests that certain fibril structures may be more likely to cause and/or influence the severity of Alzheimer's disease. The development of imaging agents that specifically target individual fibril structures will improve the reliability and specificity of diagnosis.

Lu J-X, Qiang W, Yau W-M, Schwieters CD, Meredith SC, and Tycko R. Molecular structure of β-amyloid fibrils in Alzheimer's disease brain tissue. <u>*Cell*</u> *154: 1257-1268, 2013.*

INSIGHTS INTO GENES, PROTEINS, CELLS, AND HEALTH

Increasing Mammalian Lifespan, One Gene at a Time: New research has shown that lowering the activity of a gene called *mTOR* dramatically increased the average lifespan of a group of mice and allowed them to maintain high function in several—although not all—tissue and organ systems that typically decline with age. Found in mammals, the *mTOR* gene has been implicated in such key processes as metabolism and aging. However, the mechanism of how *mTOR* reduction affects lifespan and tissue aging has not been fully understood. Previous studies showing that *mTOR* is involved in metabolic functions indicated that this gene may be connected with the increased lifespan associated with caloric restriction. In this study, researchers bred a group of mice to have genetic alterations that reduced their mTOR levels. Compared to normal mice, these mutant mice had an increased lifespan of around 20 percent, showed reduced signs of aging in many organ tissues, and, as they aged, retained more balance, grip strength, and cognitive abilities like learning and memory. Mice with reduced mTOR protein also appeared to have fewer malignant tumors than normal mice. These effects of mTOR reduction did not appear to result from altered metabolism, since mice with less mTOR had similar metabolic profiles compared to normal mice. However, these benefits did not come without a price: mTOR-deficient mice contracted more serious infections as they aged and had more pronounced bone deterioration than their normal counterparts. Together, these results suggest that tissue aging may occur on related, but separate, "clocks" or be subject to other distinct biologic regulation compared to aging of an entire organism. Further research into the mechanism of how mTOR reduction affects the body is ongoing and may guide future therapies to increase both lifespan and "health span" in humans.

Wu JJ, Liu J, Chen EB, et al. Increased mammalian lifespan and a segmental and tissue-specific slowing of aging after genetic reduction of mTOR expression. <u>*Cell Reports*</u> *4: 1-8, 2013.*

Finding Out How β-Barrels Are Built: Recent findings from the NIDDK Intramural Research Program are providing important insights about the formation of "β-barrels"—protein structures found in the exterior membranes of a large group of bacteria, many of which cause serious diseases. Most β-barrels act like pores, and many fulfill essential roles like allowing nutrients to get into the space between outer and inner membranes that is characteristic of Gram-negative bacteria. Chloroplasts—the structures inside plant cells where light is converted into chemical energy—and mitochondria—the structures in cells of both plants and animals that extract energy from a variety of fuel sources—share this double-membrane organization with Gram-negative bacteria, from which they are thought to have evolved, and also have β-barrel pores in the exterior membrane. The initial steps in the synthesis of proteins that contain β-barrels are the same as those of other proteins. The final step—insertion of the barrel portion into the outer membrane—is known to be accomplished by a group of other proteins called the "barrel-assembly machinery (BAM)" complex.

To obtain clues about how the BAM complex fulfills this role, the NIDDK scientists studied a critical component of this complex, the BamA protein, itself a β-barrel protein. They determined the three-dimensional structures of BamA from two different disease-causing bacteria and compared them to known structures of other β-barrel proteins. This approach helped them to identify unique features of BamA, and to provide likely explanations for their role in assembly of β-barrels.

The findings suggest that parts of BamA that are on the interior side of the membrane are able to bind to proteins requiring membrane insertion, to open a passage into BamA's β-barrel, and—working with another part of BamA that can move up and down in the barrel—in effect, to act like a ratchet to thread a portion of the new protein into the pore. The BamA pore itself has a feature that thins the bacterial membrane at a key point, and opens a fissure along the side of the BamA barrel, facilitating movement out of the pore and into the adjacent membrane.

The researchers hypothesize that this process repeats until all parts of the new protein needed to form a β-barrel have been properly arranged in the membrane, and the two proteins separate. The researchers also found that a simpler mechanism may be available for a subset of β-barrel proteins, where the inner, grappling/ratcheting portions of BamA might insert the new protein directly into the part of the membrane that is thinned by BamA, without actually passing through the interior of BamA's barrel. Further research will be needed to determine if these fascinating processes operate for β-barrel proteins in the outer membranes of other bacteria, or of mitochondria and chloroplasts.

Noinaj N, Kuszak AJ, Gumbart JC, et al. Structural insight into the biogenesis of β-barrel membrane proteins. Nature 501: 385-390, 2013.

Skin Strikes a Balance Between Growth and Integrity: A new study in mice has discovered that a molecule called sphingosine-1-phosphate (S1P) is an important—and sometimes vital—regulator of the skin's lifecycle. Skin cells are constantly growing, differentiating (producing specialized types of cells), dying, and being shed. Disruptions in this cycle can lead to diseases where skin is too thick or too thin. Mice lacking the gene for a protein that controls S1P had abnormally high S1P levels and stunted growth compared to normal mice when examined within a few days after birth. They also had serious skin abnormalities—the mutant animals had enhanced skin cell differentiation, which made their skin thicker than normal and prone to peeling and sloughing off. Many of these mice died by three weeks of age, and the few that survived to adulthood had skin abnormalities throughout their lives. Further analysis of the animals' skin cells demonstrated that increased S1P levels had wide-ranging effects, affecting the activity of over 700 genes, many of which are involved in skin cell differentiation. Therefore, this research suggests that S1P metabolism plays a key role in skin cell differentiation. These findings, if confirmed in humans, may lead to new treatments for skin diseases caused by abnormal skin cell differentiation, such as psoriasis.

Allende ML, Sipe LM, Tuymetova G, Wilson-Henjum KL, Chen W, and Proia RL. Sphingosine-1-phosphate phosphatase 1 regulates keratinocyte differentiation and epidermal homeostasis. J Biol Chem 288: 18381-18391, 2013.

Clinical Studies Highlight Importance of Public Biomedical Research Funding

The NIDDK is supporting clinical research studies that highlight the distinctive position that the Institute, as a public funder of medical research, can hold. Biomedical research is supported by several sources, like industry (pharmaceutical and biotechnology companies), patient advocacy organizations, private foundations, and, in the case of the NIH, the American public. Many successful collaborations have brought different funders together to maximize investments. There are also instances for each of these funders to fill a unique need in promoting research.

The following examples are studies that were designed to answer critical questions in treatment of diseases/disorders that fall under the NIDDK's purview, but were unlikely to have been undertaken by the other funding sources. They are testing generic or off-label (currently approved by the U.S. Food and Drug Administration (FDA) for a specific use or uses, but may be applicable to other uses) medications or behavioral changes and, therefore, would not be profitable to pursue. In some examples, these studies are not testing a particular therapy, but are studies of disease that may inform future therapies. Finally, many of these are large studies that require significant investment that others would simply be unable to fund. While the NIDDK is the lead sponsor of all of these studies, some have benefitted from additional contributions from others, both federal and non-federal, to help advance the research.

Diabetes Prevention and Treatment

Type 2 diabetes is a chronic and costly disease. Therefore, it is critical to determine the best and most affordable ways to prevent and treat the disease. The NIDDK recently started two diabetes trials with potentially high public health impact. Vitamin D has emerged as a potential modifier of type 2 diabetes risk. A large, randomized, and controlled clinical trial, however, is required to prove if vitamin D supplementation prevents or delays type 2 diabetes in adults who are at high risk. Because vitamin D is an inexpensive, generic supplement, it was unlikely that other funders would test its value in diabetes prevention. Therefore, the NIDDK began the Vitamin D for Type 2 diabetes (D2d) Trial, which will enroll over 2,000 participants. D2d could provide the evidence for another affordable and accessible way to help prevent or delay type 2 diabetes.

The diabetes drug metformin and/or lifestyle change are typically used as first-line treatments for type 2 diabetes, but no long-term, head-to-head comparisons have been conducted to determine the best second medication to optimize control of type 2 diabetes, and such studies were unlikely to be undertaken by other funders. The NIDDK's Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) will compare four commonly used diabetes drugs in combination with metformin. GRADE will compare the drugs for their effects on glucose levels, diabetes complications, and quality of life, along with adverse effects, over an average of nearly five years in 5,000 volunteers. The outcome of the GRADE study will have a major public health impact by establishing the most effective treatments for early therapy of type 2 diabetes, and has the potential to enable clinicians to make personalized medication decisions, based upon the individual characteristics of their patients.

The NIDDK's Look AHEAD (Action for Health in Diabetes) Trial is another trial unlikely to have been conducted by industry as it does not involve medication, but rather tests a behavioral intervention. This clinical trial, launched in 1999, was designed to evaluate the long-term effects—over a decade—of an intensive weight loss intervention in over 5,000 overweight and obese older women and men with type 2 diabetes. Look AHEAD demonstrated that the intensive lifestyle intervention resulted in sustained and clinically significant weight loss with improvements in cardiovascular risk factors as well as quality of life. Importantly, Look AHEAD determined that the intensive lifestyle intervention does not reduce cardiovascular events, such as heart attack and stroke, but did show other important health benefits such as improved diabetes control and reduced medication use. Look AHEAD continues to follow study participants to determine the long-term health impact of an intensive lifestyle intervention.

Digestive Diseases

In people with the digestive disease gastroparesis, food is slowed or stopped moving from the stomach to small intestine, leading to nausea, a feeling of fullness after eating only a small amount of food, vomiting undigested food, and lack of appetite. Tricyclic antidepressants may block certain pathways which regulate nausea and vomiting, and thus are frequently used for treatment of these symptoms in people with gastroparesis. Yet a large, randomized, and controlled trial was needed to provide evidence as to whether or not this practice benefits people with gastroparesis. Because this is not the disease for which the medication was approved, it was necessary for the clinical trial to be approved by the FDA; these conditions made it less likely that other funders would pursue such a trial. NIDDK's Nortriptyline for Idiopathic Gastroparesis (NORIG) Trial sought to evaluate whether treatment with nortriptyline, a drug used to treat depression, can improve gastroparesis symptoms. The study determined that nortriptyline did not improve overall symptoms in idiopathic gastroparesis over a 15-week period. However, improvements in appetite, satiety, and body mass index (BMI) were noted. NORIG was conducted as part of the Gastroparesis Clinical Research Consortium.

Chronic Kidney Disease

Despite the impact of chronic kidney disease on the nation's health, understanding of its epidemiology—the study of the causes, distribution, and control of disease in populations—remains incomplete. To fill this need, in 2001 the NIDDK established the Chronic Renal Insufficiency Cohort (CRIC) Study to identify risk factors that predict loss of kidney function, as well as the development and worsening of cardiovascular disease, in people with chronic kidney disease. The CRIC Study investigators recruited and are following nearly 3,900 volunteers, the largest and most comprehensive study of chronic kidney disease ever conducted. The CRIC Study investigators characterized this large cohort, contributing numerous important findings to knowledge about chronic kidney disease, and are now conducting extended follow-up of its participants. In addition, the NIDDK also supports a similar study of chronic kidney disease in children, the Chronic Kidney Disease in Children (CKiD) study. The long-term, observational nature of these studies makes them uniquely suited for NIDDK support, allowing investigators to glean new insights into the management and outcomes of chronic kidney disease.

Conclusion

Without NIDDK support, it was unlikely that these important clinical trials and studies would be conducted. In addition to filling critical gaps in knowledge, many of these efforts are collecting extra biosamples that are stored in the NIDDK's Central Repository for further research. This Web-enabled Central Repository makes biological samples and data from NIDDK-funded research available to the broader scientific community. These resources facilitate the testing of hypotheses without the need for new data generation or sample collection. Access to these NIDDK resources is an additional benefit from the public funding of important biomedical clinical trials.

SBIR and STTR Programs: Advancing Health Technology Development Through Public-Private Partnerships

The translation of basic research findings to the development and commercialization of therapeutic drugs, medical devices, and other innovative products remains a fundamental challenge for improving public health. The NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs were designed to address this issue, supporting research and development (R&D) efforts by U.S. small businesses (*i.e.*, companies with no more than 500 employees) to help develop promising and innovative health technologies.

The two programs are similar, in that they include the following objectives: using small businesses to stimulate technological innovation; strengthening the role of small business in meeting public R&D needs; increasing private sector commercialization of innovations developed through public-private partnerships; increasing small business participation in public R&D; and fostering and encouraging participation by socially and economically disadvantaged small businesses, and by and women-owned businesses.

One important difference is that for the SBIR program, the principal investigator's main employment must be with the small business itself; the STTR program has no such requirement, and thus many STTR grantees work primarily at non-profit research institutions (*e.g.*, universities) and cooperatively engage in R&D programs with private sector businesses.

The SBIR/STTR programs are structured in three phases, the first two of which are typically funded by the NIH: Phase I, which aims to establish the technical merit, feasibility, and potential for commercialization of the proposed R&D efforts and to determine the quality of performance of the small business; Phase II, which increases funding of R&D efforts initiated in Phase I, based on scientific and technical merit, as well as commercial potential; and Phase III, which, where appropriate, is for small businesses to pursue, with non-SBIR/STTR funds, the commercialization objectives resulting from the Phase I/II R&D activities. Grantees of the SBIR program are also eligible for technical assistance programs, which offer specialized, strategic business training and provide access to a vast network of industry experts. Support for research that falls within these different phases of the drug and therapy development pipeline is critically important, but has historically been underfunded—resulting in the so-called "valley of death" of investment in the drug and device development process.

Thus, the SBIR/STTR programs are important mechanisms for bridging that valley as a way to translate basic research findings to drugs, devices, and products that can benefit people. The NIDDK funds numerous SBIR/STTR grants supporting a variety of research on promising health technologies relevant to its mission. A few examples among many success stories are highlighted below.

The Sharklet Catheter

Catheter-associated urinary tract infections (CAUTIs) are the leading cause of hospital-acquired infections. CAUTIs are caused by bacteria that colonize the urinary catheter surface, leading to the formation of harmful bacterial sheets, or biofilms, over time. Sharks, unlike other marine animals, do not accumulate bacteria, algae, and other microorganisms on their skin. Shark skin is textured with diamond-shaped features, called denticles, topped with small spines.

This intriguing, naturally occurring design inspired investigators at Sharklet Technologies, Inc. to develop silicone catheters that resist biofilm formation and reduce bacterial colonization. Importantly, the innovative microbial resistance comes from the surface texture, without needing antibiotics, thus reducing the risk for the emergence of drug-resistant bacterial strains. The Sharklet catheter, supported in part by NIDDK through Phase I and II SBIR grants, successfully inhibits bacterial migration and has now been licensed to a medical device manufacturer.

HemoShear

A great number of drugs fail during the clinical trial process, often due to liver toxicity. Historically, drugs were tested for toxicity using cells grown in the laboratory and in animal models before they were tested in humans in clinical trials. These laboratory and animal systems, however, do not always reflect human liver biology accurately, allowing drugs to continue on to human trials that, after considerable time and expense, could ultimately end in failure because of toxicity.

The company HemoShear, LLC, with NIDDK Phase I and II SBIR support, developed a cell-based system that may more accurately represent the complex biology of the human liver, thereby improving the likelihood of discovering toxicity before costly and time-consuming clinical trials. HemoShear's innovative technology has the potential to save pharmaceutical companies money and time, as well as to spare patients the risk of encountering unexpected toxicity, by allowing companies to focus trials on the most safe and promising candidate drugs. Leading biotechnology and pharmaceutical companies are already working with HemoShear's system to improve their methods for evaluating the safety and efficacy of potential therapeutics.

Artificial Pancreas Technologies

When blood glucose levels are not well controlled, a person with diabetes is at much greater risk for developing devastating health complications, including blindness, kidney disease and kidney failure, nerve problems, and cardiovascular disease. An artificial pancreas, or a "closed-loop system," is technology in which a computer calculates insulin dose based on glucose levels and delivers insulin automatically through an insulin pump with minimal human input. Such technology holds great promise to help people with type 1 diabetes, as well as other populations, safely achieve recommended levels of blood glucose control.

The NIDDK has supported many aspects of research toward the development of an artificial pancreas, to a large extent through SBIR and STTR grants, for at least two decades. For example, all the current continuous glucose monitoring (CGM) technology on the market—technology that measures circulating glucose levels in real time—benefitted from NIDDK support early in development. Those technologies have been approved by the U.S. Food and Drug Administration and are currently being used by patients, but are also an important component of a future artificial pancreas system. In addition to CGM, SBIR/STTR grants support a range of other research critical for artificial pancreas development, including efforts to increase the stabilities of insulin and its opposing hormone glucagon, improve insulin delivery systems, and explore new ways to make artificial pancreas technologies more user-friendly and convenient for people with type 1 diabetes.

Conclusions

These success stories highlight the groundbreaking health technology innovations that can arise from public-private partnerships. New products that result from the SBIR/STTR programs have the potential to improve health, foster exciting new research directions, and reduce the costs of drug development and health care. The SBIR and STTR programs currently are authorized through 2017, and will continue to bridge important gaps in the pipeline of drug and medical device development.

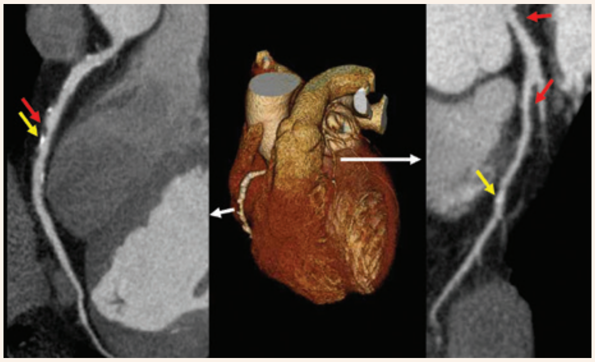
NIDDK-NIBIB's Biomedical and Metabolic Imaging Branch: Collaboration Leads to Better Imaging

In 2011, two NIH Institutes joined forces to share their expertise and sophisticated imaging tools to advance the understanding of cardiovascular disease, diabetes, and other challenging health conditions. The NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) have been conducting a joint program called the Biomedical and Metabolic Imaging Branch (BMIB) in the NIH Clinical Research Center.

The BMIB's multidisciplinary team includes imaging physicists, spectroscopists, and clinicians; the daily operations of the branch are managed by NIDDK senior radiologist Dr. Ahmed Gharib. The BMIB's high-quality imaging capabilities provide basic scientists and clinicians with a more accurate depiction of a developing disease, while low-quality images increase the likelihood of misdiagnosis.

For example, a low-resolution liver scan may leave important details—such as tiny tumors—blurry and difficult to identify. High-resolution scans, taken from many angles, however, provide clear and detailed images that enable researchers to pinpoint problems earlier in a disease. Advanced imaging techniques can also be used to examine multiple organs simultaneously, making it possible to understand, detect, and manage various systemic diseases.

Advances in imaging also allow researchers to image parts of the body faster and in greater anatomic and functional detail than ever before. BMIB researchers use a computed-tomography (CT) technique to capture crisp images of the heart's blood vessels while the heart is beating. Imaging a functioning heart is somewhat like photographing a fast-moving car—the more pictures taken, the greater the likelihood that at least one will be clear. Researchers can now capture a full CT scan of the heart in one to two heartbeats, whereas just a decade ago the same scan would have required 16 heartbeats.



BMIB's high-quality imaging capabilities provide basic scientists and clinicians with a more accurate depiction of a developing disease. Here, a three-dimensional reconstructed image of the whole heart (center) is flanked by detailed images of the right coronary artery (right) and left anterior descending coronary artery (left). The red and yellow arrows indicate different types of coronary plaques, which can be early signs of heart disease. *Photo courtesy of Dr. Ahmed Gharib, from J Clin Endocrinol Metab. 2013 May; 98(5): 2045-2052. Reprinted with permission from Nature Publishing Group.*

The BMIB's use of state-of-the-art imaging equipment and newly developed techniques benefit a variety of patients and support an expansive range of research across NIH. Proton magnetic resonance spectroscopy (MRS), for example, allows researchers to measure not only fat in the liver but also metabolites such as glycogen and choline. Studying these liver metabolites enhances the understanding of lipid and glucose metabolism under the more controlled environment of a metabolic research unit.

The BMIB grew out of NIDDK's Integrated Cardiovascular Imaging Lab, which focused its efforts on demonstrating the link between metabolic syndrome (a combination of factors that increases the risk of heart disease, stroke, and diabetes) and atherogenesis (the formation of lesions in arterial walls). Today, BMIB researchers work with the

NIDDK-led Metabolic Clinical Research Unit (MCRU) to investigate the interrelationship between obesity, coronary heart disease, and other conditions. Obese MCRU patients often go to the BMIB to be scanned in its three-tesla magnetic resonance imaging (MRI) machine that can accommodate people who weigh up to 500 pounds. The imaging techniques used on such patients allow scientists to better understand a range of metabolic diseases.

"The work that we are doing in the branch holds tremendous promise for improved understanding of systemic disease and for early detection methods [especially for] atherosclerosis, which has long been the number one killer in much of the developed world," said NIBIB Director Dr. Roderic Pettigrew. "We hope to see hospitals throughout the world one day using approaches based on this research."

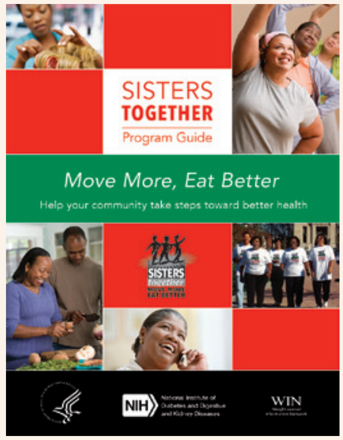
In keeping with NIH's focus on collaboration, BMIB staff scientists Drs. Ronald Ouwerkerk and Khaled Abd-Elmoniem and others work closely with other Institutes—such as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung, and Blood Institute—that also depend on advanced imaging. For example, BMIB investigators have developed MRI and MRS techniques that can assess the metabolic composition of various organs and measure tissue stiffness. High-resolution coronary MRI provides a two-fold improvement over conventional MRI in spatial resolution.

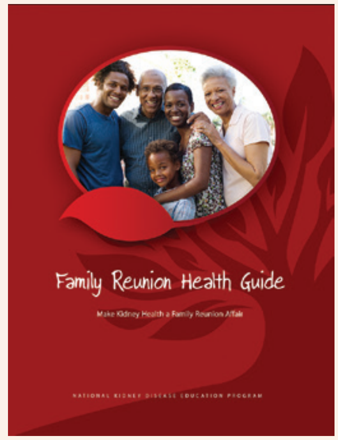
Additionally, improvements in temporal resolution allow researchers to view and measure the thickening of the coronary artery wall, the earliest stage of coronary artery disease. In the future, these new techniques may be used to monitor the effects of therapies and screen people at risk for coronary artery disease as well as metabolic and liver dysfunction.

"The collaborative infrastructure at NIH has enabled all of us to work together more efficiently," said NIDDK Director Dr. Griffin P. Rodgers. "The Biomedical and Metabolic Imaging Branch is an excellent example of what can be accomplished through ongoing partnerships within NIH."

This feature was adapted from an article that originally appeared in the May-June 2013 edition of the NIH Catalyst*.*

NIDDK Health Information Resources for the Public





The NIDDK's research mission includes some of the most common and consequential conditions affecting Americans today, as well as diseases that are more rare but nonetheless devastating. Every year, people diagnosed with these conditions and their family members ask themselves and their doctors, "What do I need to know? How can I protect my health and my family's health?"

The NIDDK is dedicated to delivering accurate, science-based health information to the public. The NIDDK offers many publications aimed at informing doctors, patients, and families affected by these conditions. A wide variety of informational materials are offered in multiple languages and often in large-print editions. To reach the widest possible audience, the publications are available as free downloads online, and printed materials can be ordered for free or at nominal cost.

All of these resources can be reached through the NIDDK Clearinghouses Publications Catalog at *www.catalog.niddk.nih.gov*

Disease-specific information is available through the:

- National Diabetes Information Clearinghouse
- National Digestive Diseases Information Clearinghouse
- National Kidney and Urologic Diseases Information Clearinghouse
- Weight-control Information Network
- National Diabetes Education Program
- National Kidney Disease Education Program
- National Endocrine and Metabolic Diseases Information Service
- National Hematologic Diseases Information Service

NIDDK Director Dr. Griffin P. Rodgers highlights the dissemination of knowledge through outreach and communication efforts as one of the overarching principles that guide his leadership and vision for the NIDDK. As Dr. Rodgers states, "We are continuing efforts to ensure that the science-based knowledge gained from NIDDK-funded research is imparted to health care providers and the public for the direct benefit of patients and their families."